(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 January 2006 (26.01.2006)

PCT

(10) International Publication Number
WO 2006/008160 A1

(51) International Patent Classification[7]: C07D 277/20, A61K 31/425

(21) International Application Number: PCT/EP2005/007958

(22) International Filing Date: 21 July 2005 (21.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0416379.6 22 July 2004 (22.07.2004) GB

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

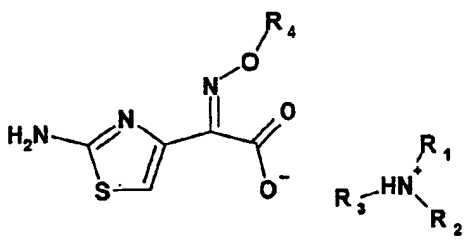
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/008160 A1

(54) Title: TERTIARY AMINE SALTS OF 2-(2-AMINOTHIAZOLE-4-YL)-2-ACYLOXYIMINO)ACETIC ACID



(I)

(57) Abstract: Subject of the present invention are crystalline tertiary amine salts of 2-(2-aminothiazole-4yl)-2-(acyloxyimino)acetic acid compounds of formula (I) wherein R_1, R_2 and R_3 independently represents unsubstituted or substituted alkyl, cycloalkyl or aryl, and R_4 denotes acyl, which may be obtained in anhydrous form. Crystalline compounds of formula I are useful in a reaction step with an activating agent in order to produce cefdinir. Additionally, a process to prepare compounds of formula I is a part of the present invention.

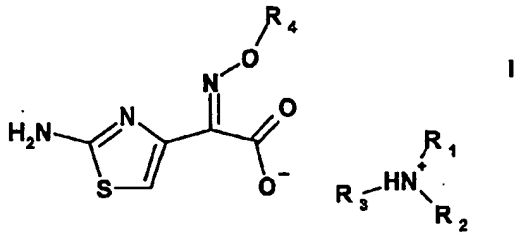
TERTIARY AMINE SALTS OF 2-(2-AMINOTHIAZOLE-4-YL)-2-(ACYLOXYIMINO)ACETIC ACID

The present invention relates to tertiary amine salts of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid in crystalline form and a process for their preparation as well as a process for the preparation of cefdinir wherein such tertiary amine salts are used.

It is known e.g. from ES 2 013 828 that a 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compounds, e.g. syn-2-(2-aminothiazol-4-yl)-2-(acetoxyimino)-acetic acid and its derivatives, may be used as an intermediate compound in the production of cefdinir, which is (*6R,7R*)-7-[[(2*Z*)-(2-Amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Usually, a process for the production of cefdinir includes a reaction step wherein a 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compound is converted into an activated form thereof such as a mercaptobenzothiazolylester, a mixed acid anhydride, an acid halide or another conventional activated form by a reaction with an activating agent. Any crystal water of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid also reacts with the activating agent and typically causes decreased yields in the activation step or/and the necessity of significantly increased amounts of activating agent, e.g. halogenation agent such as phosphorous pentachloride (see ES 2 013 828). Therefore, it is highly desirable to use anhydrous derivatives of a 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compound for an activation reaction.
However, 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compounds, for instance syn-2-(2-aminothiazol-4-yl)-2-(acetoxyimino)-acetic acid, are typically prepared from e.g. syn-2-(2-aminothiazol-4-yl)-2-(hydroxyimino)-acetic acid by reaction with alkanoic carboxylic acid anhydrides such as acetic acid anhydride under aqueous conditions and are crystallised in a hydrated form, e.g. as mono- or dihydrates. Thus, there is a need for anhydrous derivatives of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compounds.

The present invention is intended to provide novel crystalline tertiary amine salts of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compounds which are useful in a reaction step with an activating agent in order to produce cefdinir. It has surprisingly been found now that crystalline tertiary amine salts of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compounds may be obtained in an anhydrous form.

In one aspect the present invention relates therefore to tertiary amine salts of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compounds of formula



I

in crystalline form, preferably in anhydrous form, wherein R_1, R_2 and R_3 independently represents unsubstituted or substituted alkyl, cyclo-alkyl or aryl, and R_4 denotes acyl.

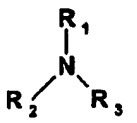
In the meaning of R_1, R_2 and R_3 alkyl includes (C_{1-12})alkyl such as (C_{1-8})alkyl, in particular (C_{1-4})alkyl, e.g. ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl or tert-butyl. Aryl includes (C_{6-12})aryl, e.g. phenyl or naphtyl, in particular phenyl. Cycloalkyl includes (C_{3-8})cycloalkyl, preferably C_3, C_5 or C_6-cycloalkyl such as cyclohexyl.

Any alkyl, cycloalkyl or aryl group of R_1, R_2 and R_3 may be unsubstituted or one to three times substituted, e.g. one times substituted by halogen or alkyl. Aryl and cycloalkyl may be also one to five times substituted by alkyl, e.g. (C_{1-4})alkyl or halogen.
In preferred embodiments of the invention R_1, R_2 and R_3 each denote n-butyl, ethyl, phenyl or n-octyl. In another preferred embodiment R_1 and R_2 denote iso-propyl and R_3 denotes ethyl. Particularly preferred are compounds wherein R_1, R_2 and R_3 each denote n-butyl. R_4 denotes acyl such as (C_{1-8})acyl, e.g. formyl, acetyl, propanoyl or butanoyl. In a preferred embodiment R_4 denotes C_2-acyl, i.e. acetyl.

If not otherwise stated herein, acyl includes (C_{1-8})acyl, e.g. formyl, acetyl, propanoyl or butanoyl, preferably acetyl.

An anhydrous form of a crystalline tertiary amine salt of formula I may contain less than 1.0% (w/w) of water, i.e. from about 0% to below 1.0% (w/w), e.g. from about 0.01% to about 0.5% (w/w) such as from about 0.05% to about 0.2% (w/w) or even less than about 0.1% (w/w).

Crystalline tertiary amine salts of formula I, e.g. in an anhydrous form, may be produced by contacting 2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid dissolved or suspended in a solvent with an amine of formula



II

wherein R_1, R_2 and R_3 are defined as in formula I. For instance a hydrate of 2-(2-aminothiazol-4-yl)-2-(acyloxyimino)-acetic acid, e.g. a monohydrate, a dihydrate or a mixture thereof, is dissolved or suspended in a solvent with an amine of formula II. Crystallisation of a tertiary amine salt of formula I may occur upon stirring the solution or suspension. If desired, measures to initiate crystallization as known in the art such as cooling, adding a counter-solvent, partly evaporation of solvent or friction of a glass stick on the surface of a glass vessel may be applied in order to accelerate and complete crystallization.

The amount of added amine of formula II is not critical. An equimolar amount of a 2-(2-aminothiazol-4-yl)-2-(acyloxyimino)-acetic acid compound dissolved or suspended in a solvent and of the amine of formula II may be used, whereby a slight molar excess of the amine of formula II, e.g. around 1.01 to around 1.50 molar equivalents of an amine of formula II per equivalent of 2-(2-aminothiazol-4-yl)-2-(acyloxyimino)-acetic acid compound may be of advantage. A higher excess, for example about 1.5 to about 5 molar equivalents of an amine of formula II per equivalent of the 2-(2-aminothiazol-4-yl)-2-(acylcarbonyloxyimino)-acetic acid compound may also be used.

The reaction temperature is not critical for the crystallization of a tertiary amine salt of formula I. Suitable reaction temperatures are from -30°C to 70°C, e.g. -20°C to 35°C, particularly from -10°C to 25°C such as at ambient room temperature. Preferably, a salt of formula I is crystallized under mild temperature conditions such as at or below ambient room temperature because that would result in a very mild and gentle dehydration process leading to high yields and very high purities of the cefdinir to be prepared from a tertiary amine salt of formula I.

Suitable solvents for the crystallisation of a tertiary amine salt of formula I, e.g. in an anhydrous form, are solvents which may typically be used for crystallisation of amine salts of beta-lactam compounds. Suitable solvents may include ketones, e.g. (C_{3-6})-ketones, nitriles, such as (C_{1-6})-nitriles, ethers, for example (C_{2-6})alkyl(C_{2-6})alkylethers or tetrahydrofuran (THF), amides such as dimethylacetamide or dimethylformamide and chlorinated hydrocarbons such as methylenechloride, and mixtures of two or more of said solvents. Preferred solvents are acetone, THF and N,N-dimethylformamide.

Counter-solvents which may optionally be added to facilitate crystallisation are liquids which, if added, decrease the solubility of a tertiary amine salts of formula I. Suitable counter-solvents are aliphatic, alicyclic or aromatic hydrocarbons such as (C_{5-18})alkanes, (C_{5-10})cycloalkanes or benzene that may be unsubstituted or substituted by (C_{1-6})alkyl, e.g. toluene, xylene, mesitylene or carboxylic acid esters such as acetic acid-(C_{1-4})-alkyl esters, e.g. n-butylacetate or ethylacetate.

The starting 2-(2-aminothiazol-4-yl)-2-(acyloxyimino)-acetic acid compounds, e.g. in the form of hydrates may be produced by known methods.

In another aspect the present invention relates to a process for the production of cefdinir comprising the steps

a. preparing a tertiary amine salt of formula I in crystalline form, preferably in an anhydrous form, as described above,
b. reacting the crystalline amine salt obtained from step a. with an activating agent to obtain a 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compound in an activated form,
c. reacting the activated 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compound obtained from step b. with a 7-amino-3-vinyl-3-cephem-4-carboxylic acid compound to obtain a 7-[2-(2-aminothiazole-4-yl)-2-(acyloxyimino)-acetylamino]-3-vinyl-3-cephem-4-carboxylic acid compound, and
d. splitting off the acyl-group at the imino group from a compound as obtained in step c. to obtain cefdinir.

The preparation of a tertiary amine salt of formula I in step a., e.g. in anhydrous form, may be carried out as described above. Step b. may be carried out in analogy, e.g. according to methods known in the art, e.g. in analogy to a process as described in WO 2004/016623. An activated form includes a mercaptobenzothiazolylester, a mixed acid anhydride, an acid halide such as an acid chloride or other conventional activated forms. Examples of activating agents are bis-(benzothiazol-2-yl)-disulphide/triethylphosphite, bis-(benzothiazol-2-yl)-disulphide/triphenylphosphine, phosphorous pentachloride, pivaloyl chloride/triethylamine etc. Step c. may be carried out in analogy, e.g. according to known methods.
Step d. may be effected in analogy to, e.g. according to methods known in the art, for instance by hydrolysis or alcoholysis with a strong acid. If step d. is performed by alcoholysis, it is desirous to use water-free strong acids. Suitable strong acids include strong

organic acids such as trifluoroacetic acid, sulfonic acids such as methanesulfonic acid, benzenesulfonic acid or a toluene sulfonic acid, a sulfamic acid and water-free anorganic acids, e.g. sulphuric acid. Cleavage of the acetyl-group is usually carried out in a solvent which does not adversely affect the reaction. Suitable solvents include alcohols such as methanol, ethanol, propanols, butanols. The reaction is carried out at temperatures from -20 to 30°C, preferably between -5 and +10°C. Typically an excess of anhydrous acid, e.g. from 1.1 to 5.0 molar equivalents are used.

In another aspect the present invention relates to a process for the production of an activated form of 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compounds comprising the steps of preparing a tertiary crystalline amine salt of formula I, e.g. in an anhydrous form, as defined above and reacting the obtained crystalline tertiary amine salt of formula I with an activating agent in order to obtain a 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compound in an activated form.

A tertiary amine salt of formula I in crystalline form, preferably in an anhydrous form, e.g. prepared by a process as set out above, is useful for the production of an activated form of 2-(2-aminothiazole-4-yl)-2-acylimino acetic acid compounds. An activated form of 2-(2-aminothiazole-4-yl)-2-acylimino acetic acid compounds includes for example an acid halide such as an acid chloride, a mixed acid anhydride and a mercaptobenzothiazolyl ester or other conventional activated forms resulting from reactions with activating agents such as those listed above.

Therefore, the present invention relates in another aspect to the use of a tertiary amine salt of formula I in crystalline form, e.g. in an anhydrous form, in the preparation of an activated form of 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compounds.

A tertiary amine salt of formula I in crystalline form, preferably in an anhydrous form, e.g. prepared by a process as set out above, is useful as an intermediate in the production of cefdinir.

Therefore, the present invention relates in a further aspect to the use of a tertiary amine salt of formula I in crystalline form, e.g. in an anhydrous form, in the production of cefdinir.

The following Examples will indicate the different aspects of the present invention and are in no way intended to limit the scope of the present invention. All temperatures are given in °C.

Abbreviations:

MeOH: Methanol

HMDS: Hexamethyldisilazane

TMSI: Trimethyliodsilane

EtOH: Ethanol

TsOH: Toluene sulfonic acid

DMAc: Dimethylacetamide

Example 1

(6R,7R)-7-[[(2Z)-(2-Amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Cefdinir)

A solution of 21.1 g of 7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid in the form of a salt with *ortho*-phosphoric acid in 80 ml of MeOH is mixed at 0° with 3.9 ml of concentrated H_2SO_4, the mixture obtained is stirred at ≤10° and added dropwise to a solution of 17.5g $NaHCO_3$ in 600ml of water. The pH value of the mixture obtained is adjusted to pH 5.3, 1.8 g of activated carbon are added, the mixture is stirred, and the activated carbon is filtered off and washed with H_2O. The filtrate obtained is heated to 25° to 30° and the pH value is adjusted to pH 3 with 2n H_2SO_4. (*6R,7R*)-7-[[(2Z)-(2-Amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid crystallises, is filtered off, washed and dried.

Weighed product: 12.08 g.

Example 2

Tri-(n-butyl)ammonium (syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate)

25.0g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid dihydrate (water content: 14.5%) are suspended in 100 ml of acetone at ambient temperature and 24.4ml of tri-(n-butyl)amine are added. The material dissolves and immediately begins to crystallize again. The mixture is cooled to -10°C and stirred at this temperature for 30 minutes. The cristalline material is filtered, washed with a small portion of cold acetone and dried in vacuum.

Weighed product: 32.7g

H_2O: 0.1%

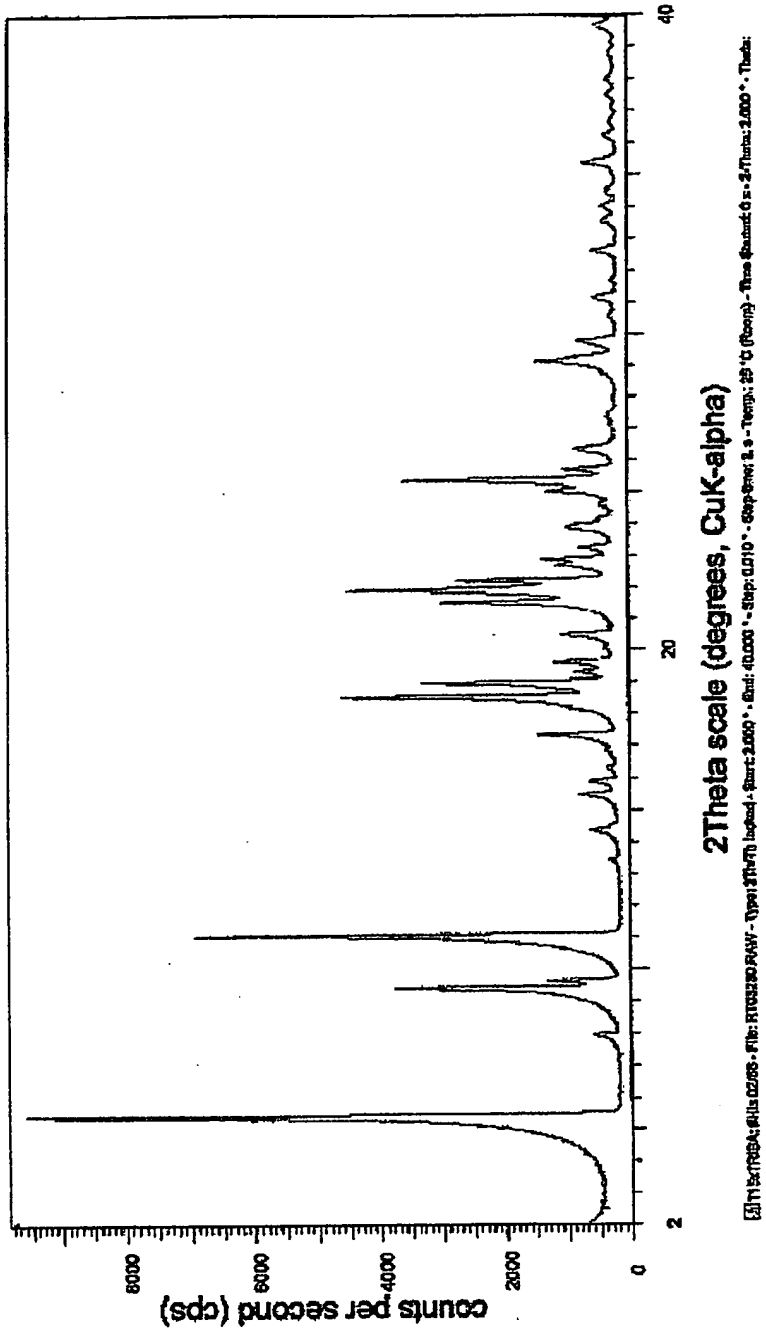
^{1}H-nmr($CDCl_3$) δ 0.87(t,9H,J=7.4Hz), 1.29(m,6H), 1.58(m,6H), 2.08(s,3H), 2.89(m,6H), 6.78(s,1H), 7.55(br s,2H)

IR(golden gate): 3431, 3109, 2959, 2873, 1750, 1608, 1375, 1227 cm^{-1}

mp: 105 °C (decomposition)

X-ray diffraction pattern see figure 1

Figure 1: X-ray diffraction pattern of *tri-(n-butyl)ammonium (syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate) prepared according to Example 2;
Analytical XRD equipment: Powder X-ray diffractometer AXS-BRUKER D-8; Cu-target (wavelength CuKα1,2 : =.15406 nm), scintillation counter, parallel beam optics, theta/theta coupled, 9 position sampler changer; operating conditions: 40kV, 40mA,continuous scan 2-40° theta/2Theta; step size 0.01 steps per second, counting time 2 seconds, room conditions; sample preparation: standard sample holders



Example 3

Tri(n-butyl)ammonium (syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate)

5.0g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid monohydrate (water content: 8.0%) is suspended in 20 ml of acetone at ambient temperature and 5.2 ml of tri-(n-butyl)amine are added. The material partly dissolves and immediately begins to crystallize again. The mixture is cooled to -10°C and stirred at this temperature for 60 minutes. The crystalline material is filtered, washed with a small portion of cold acetone and dried in vacuum.

Weighed product: 7.2g

H_2O: 0.5%

Other physical and spectroscopic data identical as described in example 2.

Example 4

Tri-(n-butyl)ammonium (syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate)

5.0g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid dihydrate are dissolved in 20 ml of N,N-dimethylformamide at ambient temperature and 5.8ml tri-(n-butyl)amine is added. The clear solution is cooled to 0°C and white crystals are formed. 200ml acetone are added and the resulting crystal suspension is cooled to -10°C and stirred at this temperature for 60 minutes. The crystalline material is filtered, washed with a small portion of cold acetone and dried in vacuum.

Weighed product: 5.7g

H_2O: 0.1%

Other physical and spectroscopic data identical as described in example 2.

Example 5

Triethylammonium (syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate)

5.0g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid dihydrate are dissolved in 20 ml of N,N-dimethylformamide at ambient temperature and 3.4ml of triethylamine are added. The material begins to crystallize and 200ml acetone are added. The mixture is cooled to 0°C and stirred at this temperature for 30 minutes. The crystalline material is filtered, washed with a small portion of cold acetone and dried in vacuum.

Weighed product: 5.7g

H_2O: 0.3%

^{1}H-nmr(CD_3OD) δ 1.30(t,9H,J=7.4Hz), 2.19(s,3H), 3.21(q,6H,J=7.4Hz), 7.08(s,1H)
IR(golden gate): 3302, 3096, 2987, 1756, 1613, 1536, 1384, 1356, 1206 cm^{-1}
mp: 104 °C (decomposition)

Example 6

Diisopropylethylammonium (syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate)

5.0g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid dihydrate are dissolved in 20 ml of N,N-dimethylformamide at ambient temperature and 4.2ml of diisopropylethylamine are added. The material begins to crystallize and 200ml acetone are added. The mixture is stirred at this temperature for 60 minutes. The crystalline material is filtered, washed with a small portion of acetone and dried in vacuum.
Weighed product: 6.3g
H_2O: 0.2%
^{1}H-nmr(CD_3OD) δ 1.35(m,15H), 2.19(s,3H), 3.20(q,2H,J=7.3Hz), 3.70(m,2H), 7.06(s,1H)
IR(golden gate): 3244, 3111, 2986, 1752, 1613, 1541, 1387, 1363, 1218 cm^{-1}
mp: 110 °C (decomposition)

Example 7

Tri(n-octyl)ammonium (syn-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate)

5.0g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid dihydrate are suspended in 100 ml of acetone at ambient temperature and 9.7ml of tri-(n-octyl)amine is added. The material dissolves and the mixture is cooled to -20°C for crystallisation and stirred at this temperature. The crystalline material is filtered, washed with a small portion of cold acetone and dried in vacuum.
Weighed product: 8.2g
H_2O: 0.2%
^{1}H-nmr($CDCl_3$) δ 0.82(t,9H,J=6.8Hz), 1.22(m,30H), 1.61(m,6H), 2.09(s,3H), 2.89(m,6H), 6.79(s,1H), 7.55(br s,2H)
IR(golden gate): 3427, 3100, 2924, 2855, 1757, 1612, 1365, 1216 cm^{-1}
mp: 90 °C (decomposition)

Example 8

Syn-2-(2-Aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzothiazolylester

12.7 g crystalline anhydrous tri(n-butyl)ammonium (*syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetate) (water content 0.1% by weight) are dissolved at room temperature in 70 ml of methylene chloride and then cooled to 0°C. The solution is mixed with 13.2g of bis-(benzothiazol-2-yl)-disulphide and stirred thoroughly for 5 minutes. In a period of 20 minutes, 7.3ml of triethylphosphite are dispensed in and the solution is stirred vigorously for ½ hours at 0°C, subsequently cooled to -15°C and stirred for a further 1½ hours. The yellowish crystalline product is filtered, washed three times, each time with 20 ml cold methylene chloride, and dried over night in a vacuum at 30°C.

Weighed product: 11.2g

^{1}H-nmr(DMSO-d_6) δ2.22(s, 3H), 7.36(s, 1H), 7.48(br s, 2H), 7.59(m, 2H), 8.09(m, 1H), 8.22(m, 1H)

Example 9

7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.*para*-toluenesulfonate

15.0g 7-amino-3-vinyl-3-cephem-4-carboxylic acid are suspended in 150ml dichloromethane and the mixture heated to boiling. 13.6ml HMDS and 10µl TMSI are added and the mixture heated for 2h under reflux conditions and passing a nitrogen stream through the solution. The clear solution is cooled to 30°C and mixed with 30ml DMAc. 27.6g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino) acetic acid -mercaptobenzthiazolylester is added in 1 portion and stirred for 3h at 30°C. The reaction mixture is added dropwise to a solution of 16.40g TsOH.hydrate in a mixture of 31.5ml EtOH and 7.2ml water. The product crystallizes out. The suspension is diluted with 360ml methylene chloride and stirred for 60min at 0°C. The crystalline product is filtered off and washed three times, each time with 75ml cold methylene chloride, and dried under vacuum at 30°C.

Yield: 39.32g

^{1}H-nmr(DMSO-d_6) δ 2.21(s,3H), 2.28(s,3H), 3.61&3.89(ABq, 2H,J=17.7Hz), 5.25(d,1H,J=4.8Hz), 5.32(d,1H,J=11.4Hz), 5.61(d,1H,J=17.5Hz), 5.84(dd,1H,J=4.8&7.9Hz), 6.92(dd,1H,J=11.1&17.4Hz), 7.12&7.48(AA'BB'm,4H), 7.22(s,1H), 10.04(d,1H,J=7.9Hz)

Toluenesulfonic acid: 26.0%

Mp: 145°C (decomposition).

Example 10

7-[2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)acetamido]-3-vinyl-cephem-4-carboxylic acid.phosphate

21.43g 7-amino-3-viny-3l-cephem-4-carboxylic acid are suspended in 214ml dichloromethane, mixed with 15.68ml HMDS and 29µl TMSI at RT and heated for 2h under reflux conditions and passing a nitrogen stream through the solution. The mixture is cooled to 30°C and 42.9ml DMAc and 39.4g *syn*-2-(2-aminothiazol-4-yl)-2-(methylcarbonyloxyimino)-acetic acid-mercaptobenzthiazolylester are added. The mixture is stirred for 2.0 h at 30°C, cooled to 0°C and the reaction mixture added dropwise at 0°C to a solution of 7.0ml 85% phosphoric acid in 53.6ml MeOH and 11.2ml water, on which a thick crystalline suspension is formed. The suspension is diluted with 257ml methylenechloride, stirred for 1h at 0°C and filtered. The filter cake is washed once with a mixture of 90ml methylenechloride and 17ml MeOH, and then twice more, each time with 107ml methylenechloride, followed by vacuum drying at ambient room temperature.

Yield: 42.60g

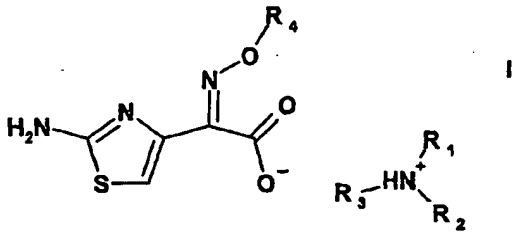
^{1}H-nmr(DMSO-d_6) δ 2.17(s,3H), 3.59&3.88(ABq, 2H,J=17.6Hz), 5.23(d,1H,J=4.8Hz), 5.31(d,1H,J=11.4Hz), 5.60(d,1H,J=17.5Hz), 5.82(dd,1H,J=4.8&8.0Hz), 6.90(dd,1H,J=11.2&17.6Hz), 7.08(s,1H), 9.91(d,1H,J=8.0Hz)

H_3PO_4: 16.9%

Mp: 170°C (decomposition)

Claims

1. A tertiary amine salt of 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid in crystalline form of formula



I

wherein R_1, R_2 and R_3 independently represents unsubstituted or substituted alkyl, cyclo-alkyl or aryl, and R_4 denotes acyl.

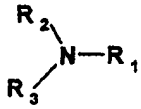
2. The compound according to claim 1 wherein R_1, R_2 and R_3 each denote n-octyl, n-butyl, phenyl or ethyl, or wherein R_1 and R_2 each denote iso-propyl and R_3 denotes ethyl.

3. The compound according to claim 1 or claim 2 in an anhydrous form.

4. The compound according to claim 3 with a water content of below 1%(w/w).

5. The compound according to any one of claims 1 to 4 wherein R_4 is acetyl.

6. A process for the preparation of a crystalline tertiary amine salt of formula I as defined in claim 1 comprising the step of bringing an amine of formula



II

wherein R_1, R_2 and R_3 are as defined in claim 1,
into contact with a suspension or solution of a 2-(2-aminothiazole-4-yl)-2-(acyloxyimino)acetic acid compound in a solvent to obtain an amine salt of formula I in crystalline form.

7. The process according to claim 6 wherein a 2-(2-aminothiazole-4-yl)-2-(acylimino)acetic acid compound in the form of a hydrate is dissolved or suspended before it is contacted with the amine of formula II.

8. A process for the production of cefdinir comprising the steps
   a. preparing a tertiary amine salt of formula I in crystalline form as defined in any one of claims 1 to 5,
   b. reacting the crystalline amine salt obtained from step a. with an activating agent to obtain 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid in an activated form,
   c. reacting the activated 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid obtained from step b. with 7-amino-3-vinyl-3-cephem-4-carboxylic acid to obtain a 7-[2-(2-aminothiazole-4-yl)-2-(acyloxyimino)-acetylamino]-3-vinyl-3-cephem-4-carboxylic acid, and
   d. splitting off the acyl-group at the imino group from a compound as obtained in step c. to obtain cefdinir.

9. The process according to claim 8 wherein the activated form of a 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compound is a mercaptobenzothiazolylester, an acid halogenide or a mixed acid anhydride.

10. A process for the production of an activated form of a 2-(2-aminothiazole-4-yl)-2-acyloxyimino acetic acid compound wherein a tertiary amine salt of formula I as defined in any one of claims 1 to 5 is prepared and then reacted with an activating agent.

11. Use of a tertiary amine salt of formula I in crystalline form as defined in any one of claims 1 to 5 in the production of an activated form of a 2-(2-aminothiazole-4-yl)-2-acylimino acetic acid compound.

12. Use of a tertiary amine salt of formula I in crystalline form as defined in any one of claims 1 to 5 in the production of cefdinir.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/007958

A. CLASSIFICATION OF SUBJECT MATTER
C07D277/20 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/016623 A (SANDOZ GMBH; KREMMINGER, PETER; WOLF, SIEGFRIED; LUDESCHER, JOHANNES) 26 February 2004 (2004-02-26) page 8, line 16 - page 8, line 19 examples 2,3 claim 9 the whole document	1-12
Y	EP 0 185 220 A (F. HOFFMANN-LA ROCHE & CO. AKTIENGESELLSCHAFT) 25 June 1986 (1986-06-25) Formelschema I (Verbindungen der Formel VIII), Column 4, lines 19 and 20 Example (Beispiel), Step c), column 7, lines 7 and 8	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 December 2005	15/12/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Deutsch, W

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/007958

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 340 751 A (FUJISAWA PHARMACEUTICAL CO., LTD) 3 September 2003 (2003-09-03) the whole document examples 1,2	1-12
A	EP 0 531 981 A (BRISTOL-MYERS SQUIBB COMPANY) 17 March 1993 (1993-03-17) the whole document page 5, formula III	1-12
A	ES 2 013 828 A6 (FUJISAWA PHARMACEUTICAL CO., LTD) 1 June 1990 (1990-06-01) cited in the application the whole document	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/007958

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004016623 A	26-02-2004	AU 2003255424 A1	03-03-2004
		EP 1554289 A1	20-07-2005
EP 0185220 A	25-06-1986	JP 61145187 A	02-07-1986
EP 1340751 A	03-09-2003	AU 2255302 A	18-06-2002
		CA 2430840 A1	13-06-2002
		CN 1479730 A	03-03-2004
		WO 0246175 A1	13-06-2002
		US 2004034233 A1	19-02-2004
EP 0531981 A	17-03-1993	AT 209209 T	15-12-2001
		AU 655838 B2	12-01-1995
		AU 2284492 A	11-03-1993
		BG 61189 B1	28-02-1997
		CA 2077836 A1	11-03-1993
		CN 1070398 A	31-03-1993
		CN 1158333 A	03-09-1997
		CZ 9202780 A3	17-03-1993
		CZ 9600719 A3	11-06-1997
		DE 69232216 D1	03-01-2002
		DE 69232216 T2	27-06-2002
		DK 531981 T3	21-05-2002
		EG 20184 A	30-09-1997
		ES 2165351 T3	16-03-2002
		FI 924031 A	11-03-1993
		FI 20011921 A	01-10-2001
		HU 62901 A2	28-06-1993
		IL 103109 A	13-07-1997
		JP 3434840 B2	11-08-2003
		JP 5194532 A	03-08-1993
		KR 178280 B1	20-03-1999
		MX 9205147 A1	01-03-1993
		NO 923495 A	11-03-1993
		NZ 244295 A	28-08-1995
		OA 9764 A	30-11-1993
		PH 31206 A	05-05-1998
		PL 295873 A1	04-05-1993
		PT 531981 T	31-05-2002
		RO 109651 B1	28-04-1995
		SK 33698 A3	12-09-2000
		SK 278092 A3	12-09-2000
		RU 2042681 C1	27-08-1995
		ZA 9206866 A	09-03-1993
ES 2013828 A6	01-06-1990	CA 1340604 C	22-06-1999
		JP 2000790 A	05-01-1990
		JP 2600878 B2	16-04-1997
		KR 140887 B1	01-06-1998